ExAblate® -- 1.5 and 3.0T
Model 2000, 2100 (Cradle Type 1.0, 1.1), 2100 V1 (Cradle Type 1.01, 1.11)

INFORMATION
FOR
PRESCRIBERS

System Software Version 6.2

October – 2012

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InSightec

ExAblate® (1.5 and 3T) System

INFORMATION FOR PRESCRIBERS

Caution	**FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN WHO HAS COMPLETED TRAINING IN THE USE OF THE DEVICE.**

Read all instructions, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury.

Training in both magnetic resonance imaging and use of the ExAblate are critical to ensure proper performance and safe use of this device.

Physicians should contact their local InSightec representative prior to initial use of the ExAblate to obtain information about training and receive team training requirements.

1.0 LABELING AND CLINICAL RESULTS

1.1 DEVICE DESCRIPTION

1.1.1 Device Name and Configuration

The device full name and configuration is summarized in the table below:

Device Name			
Generic Name	**MRgFUS**		
System	**ExAblate**		
Model	**2000**	**2100**	
Version		**0**	**1**
Cradle Type		**1.0 / 1.1**	**1.01 / 1.11**
Application	**Bone**		

The ExAblate system for this indication will also be marketed under

- "MRgFUS ExAblate ONE" with the following logo:

- "MRgFUS ExAblate OR" with the following logo:

1.1.2 Overview

The ExAblate System is a device that can target and ablate soft tissue without requiring a surgical incision, using a technique called magnetic resonance image guided focused ultrasound surgery (MRgFUS). The ExAblate treatment of painful bone metastases utilizes the acoustic properties of bone to absorb ultrasound energy to achieve palliation; bone has approximately 50 times higher acoustic absorption of ultrasound energy as compared to soft tissue and allows minimal penetration of the ultrasound energy.

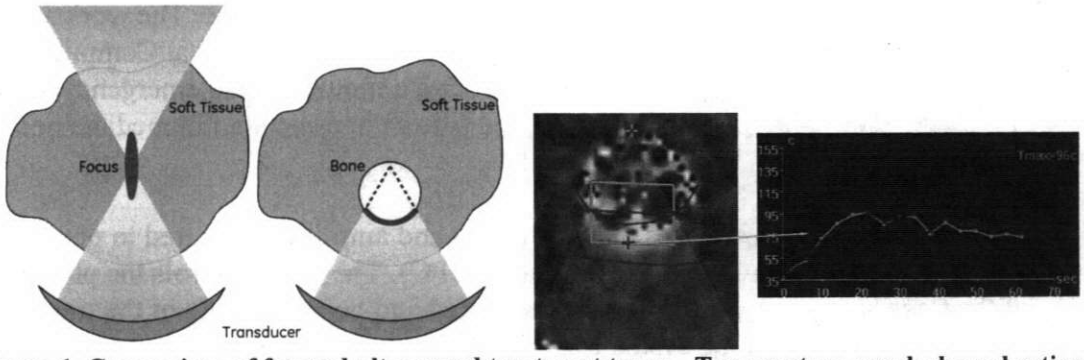


Figure 1 Comparison of focused ultrasound treatment types. Temperature graph shows heating of bone-soft tissue interface of a pig femur.

The bone metastasis treatment utilizes the concept of the "wide beam approach." With this approach an imaginary focus (target) is placed on the distal side of the bone to the transducer. The intersection of the focused ultrasound beam with the bone cortex creates a larger ablation area compared to placing the focus directly on the bone cortex as in soft tissue ablation. By applying ultrasound energy to the bone surface creates a temperature rise in the part of the bone cortex enclosed in the beam path-zone, thus indirectly ablating the adjacent periosteum (**Figure 1**). The tight focusing of the ExAblate is designed to limit the ablation to the targeted region and minimize the heating of tissue outside the target.

As the treatment is performed, the *MR thermal mapping* displays the change in tissue temperature as an overlay on the anatomic image, creating a thermal "map" that changes over time as the tissue is heated, then cools.

The hardware and software components of the ExAblate are described below.

1.1.3 Hardware

The basic ExAblate system is comprised of three main components:

- Patient Table
- Operator console
- Equipment Cabinet

The patient table, on which the patient lies during treatment, is composed of two parts: the table and the cradle. The cradle houses the focused ultrasound transducer in an acoustically transparent fluid (e.g. water or light oil) bath, as well as the motors that move the transducer. The table houses the power modules that activate elements of the transducer and elements of a cooling system for the bath fluid. The patient table is compatible with high field (1.5T and 3T) MR scanners made by General Electric (GE – Milwaukee).

The workstation is a computer that has the ExAblate® software installed. The operator controls the ExAblate® using graphical interface based software. The workstation communicates user requests and commands to the Control Personal Computer (CPC). The workstation also has a monitor, a keyboard, a mouse and an emergency stop sonication button that cuts the power to the system in case of an immediate need to stop the sonication.

The equipment cabinet houses the electronics and amplifiers required to power the system, along with the Control Personal Computer (CPC). The CPC controls the physical motion of the transducer, coordinates the power output and beam forming of the transducer, and controls the water cooling system.

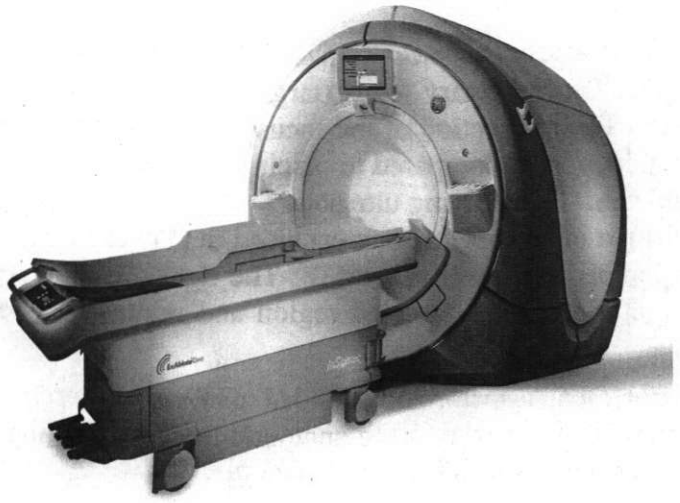


Figure 2 ExAblate Patient Table docked to the MR scanner

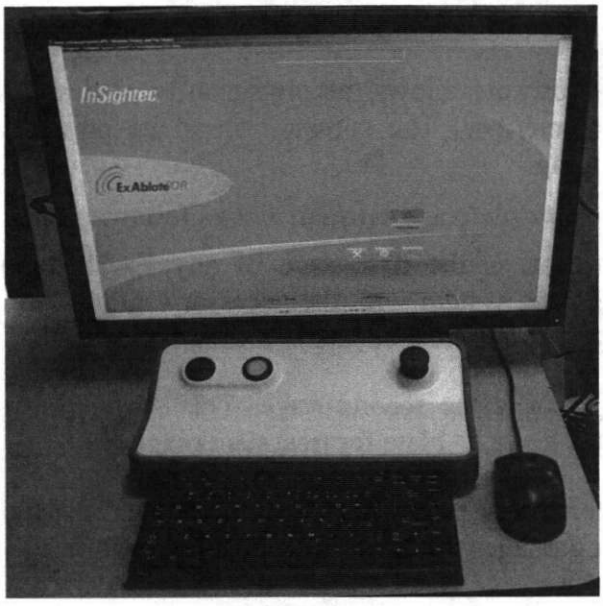


Figure 3 ExAblate Operator Console

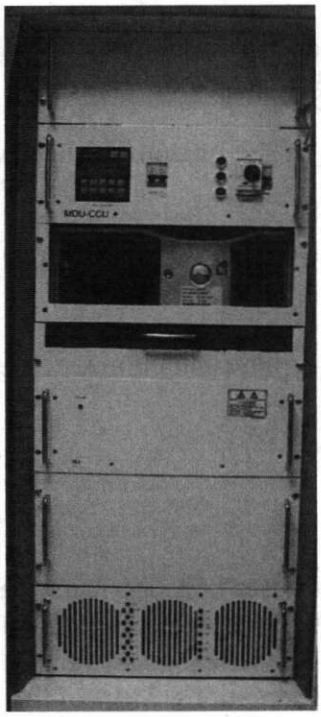


Figure 4 ExAblate Equipment Cabinet (Left), and ExAblate Cooling System (Right)

1.1.4 Software

The ExAblate software allows the physician to plan and execute the treatment using a graphical user interface. The software steps the physician through each stage of the treatment planning.

These steps to complete a treatment are as follows:

- **Calibration** is the first stage of any ExAblate treatment session. This stage provides the system with the necessary information to register patient, MR scan plane and therapy transducer coordinates.

- **Load Data** is the second stage. This stage transfers the images from the MR system to the ExAblate for treatment planning.

- **Register Stage** provides CT-MR registration, which will align the CT and MR planning images to assist in bone cortex definition

- **Draw** stage provides many tools with which to plan the course of a therapy session. This process begins with the definition of the region of treatment (ROT), skin line, other sensitive body landmarks, tissue contours, and the selection of a specific treatment protocol.

- **Plan** stage is where the system automatically creates a treatment plan based on the ROT prescribed and treatment protocol selected.

- **Verify** stage includes the confirmation of the anatomical accuracy aspects of the treatment.

- **Treat** stage is the actual delivery of energy to each of the planned locations for ablation of the planned region of treatment.

For more detailed information about each of these functions, refer to the ExAblate Operator's Manual.

1.1.5 Graphical User Interface (GUI)

The GUI, shown in **Figure 5,** was designed to be user friendly, using mostly buttons, icons, graphical representations and annotations and overlays directly on the MR image. For example, the skin line, region of treatment, individual sonications and beam path overlaid on MR images in three perpendicular orientations. Most of the treatment operations can be performed using the mouse with minimal manual data entry.

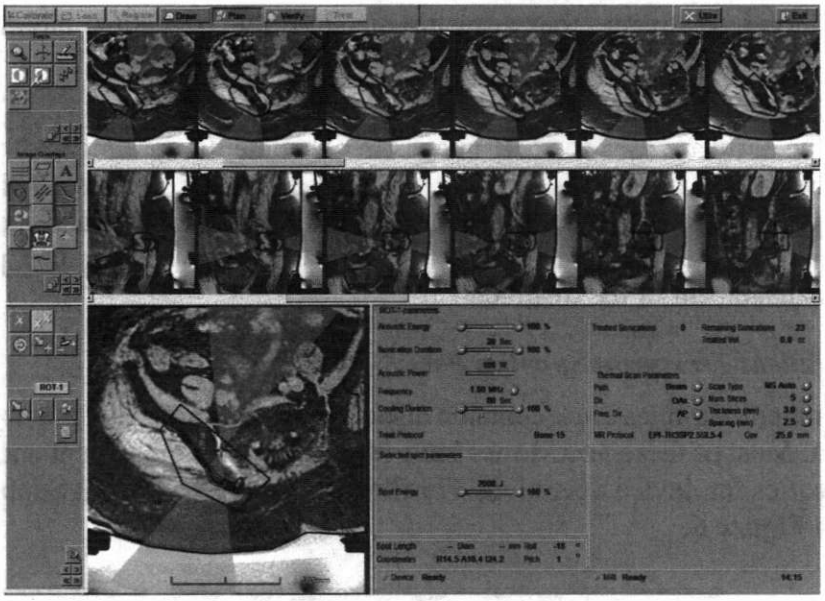


Figure 5 ExAblate Software Graphical User Interface: 1) Graphical user interface uses buttons and icons to identify functions during treatment, 2) the software overlays graphical displays on MR image(s), 3) treatment parameters and treatment progress easily accessible for continuous tailoring and monitoring of the treatment.

Dialogue boxes and tool tips that appear when the cursor hovers over a button assist the user at every stage.

- **Image acquisition**
  The software communicates with the MR-computer software to acquire planning images, and MR phase images during treatment.
- **Imaging tools**
  Image enhancing operations, such as zoom in/out, image contrast and measurement tools, can be used on MR images during the treatment planning and delivery.
- **Safety mechanisms**
  Safety mechanisms are built into the software preventing the physician from bypassing steps necessary for a safe treatment. For example, the skin line must be drawn before the system can create a sonication plan, and fiducial markers denoting anatomical structures must be placed before verification of treatment geometry and dosimetry.
- **Sonication parameters and status**
  Treatment parameters are set using pre-planned protocols. Within a limited range, the energy level, sonication and cooling duration, spot size, etc., may be adjusted during the course of the treatment. The software also keeps track of the status of each sonication (including energy delivered, elapsed time, and thermal dose volume - **Figure 5**).

- **Cavitation / Reflection monitoring**
  During treatment, the software displays the reflection monitoring graph and cavitation spectrum to the physician.
- **Thermal Thermometry**
  The software uses the MR images to calculate thermal maps. It then displays this thermal map as an overlay on the anatomic images. This provides both quantitative feedback, in the form of a time/temperature and thermal dose graph, and qualitative feedback, as a color map, to assist the physician in the management of the treatment.

1.1.6 Patient Treatment Supplies Pack

The Treatment Supplies Pack contains disposable accessories that are used for each treatment. Most of these accessories have no contact with the patient and are used strictly as accessories for device operation. For illustration, the Treatment Supplies Pack is shown in **Figure 6**.

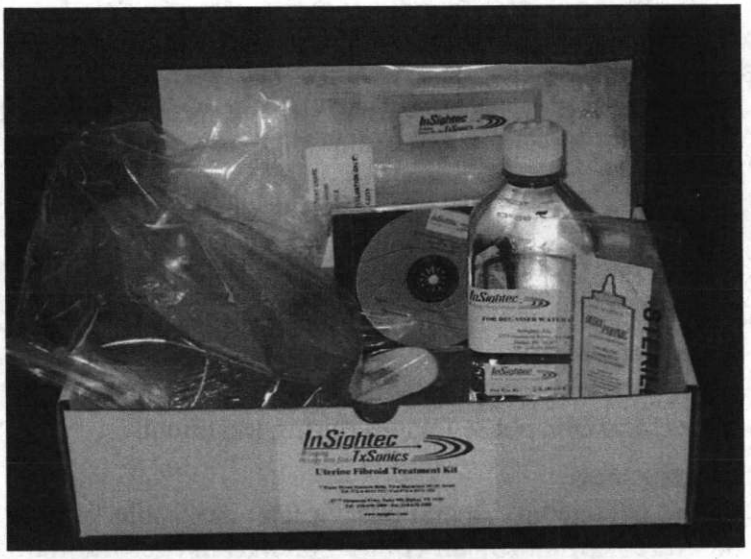


Figure 6: Treatment Supplies Pack - for illustration

- Various shapes of Gel Pad for acoustic coupling – these are hypoallergenic, flat gel pads that provide acoustic coupling to the relevant body part. The gels are biocompatible and conform to appropriate standards.
- Degassed water (1 liter) - Mineral free, degassed water to prevent calcium deposits on the patient table and to prevent microbubble formation during treatment.
- Ultrasound Gel - hypoallergenic water-soluble aqueous coupling agent to provide acoustic coupling between Mylar and transducer drape.
- Transducer Drape - Highly tear-resistant, hypoallergenic, acoustically transparent 30" by 30" plastic drape used to create acoustic coupling in the water bed. The drape is biocompatible and conforms to appropriate standards.

- Plastic Scraper - A plastic scraper to facilitate positioning of transducer drape and eliminate air bubbles and folds.
- Recordable CD (Optional) - Blank CD to record and store patient treatment information at end of procedure (if requested by site or for clinical trials).
- Cleansing Cloth (Optional) - Disposable cloth for cleaning off the ultrasound gel.

1.2 INTENDED USE / INDICATIONS FOR USE

The ExAblate is indicated for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible

1.3 PATIENT SELECTION CRITERIA FOR TREATMENT WITH EXABLATE

1.3.1 Patient Selection Criteria

- Definitive diagnosis of a bone metastasis as the source of pain symptoms
- Able to fit into MRI unit
- Able to tolerate the procedure with or without some form of sedation (e.g.: conscious sedation) and / or adequate level of local pain control; e.g.: nerve block or local anesthesia
- Able to communicate sensations to the physician during the procedure
- Able to activate **Stop Sonication** button

1.3.2 Contraindications

The ExAblate treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, weight >110 kg, allergies to MR contrast agent etc.
- Patients who need pre-treatment surgical stabilization of the affected bony structure or targeted tumor is in impending fracture
- Women who are pregnant.
- Patient with extensive scarring in an area in the path of energy planned passage to the treatment area
- Patient when sensitive organs or other interfering body structures within the path of the ultrasound beam (e.g., scar, skin fold or irregularity, bowel, other bone, surgical clips, or any hard implants) from the path of the ultrasound beam.
- Targeted tumor is in the skull or less than 1 cm from the skin surface
- Patients with advanced kidney disease or on dialysis

- Individuals who are not able or unwilling to tolerate the required prolonged stationary position during treatment (approximately 2 hrs)

1.3.3 Warnings

- The transducer interface (gel pad and water) must be in complete contact with the patient's skin without gaps to avoid skin burns. Monitor the "reflection" display throughout treatment for skin folds, bubbles or loss of complete contact between the gel pad and the skin to avoid potential burns.
- Ensure that the patient can activate the **Stop Sonication** button before initiating treatment. In the event of pain or patient motion, failure to do so may result in serious injury.
- Accurate calibration of the alignment of the transducer at the start of the treatment is critical to accurate targeting and to avoid injury to non-targeted tissue. Perform geometrical verification prior to treatment to ensure proper alignment before beginning treatment.
- Cavitation and reflection can result in serious injury to non-targeted tissue. Both reflection and cavitation should be constantly monitored throughout the treatment.
- Failure to monitor the MR thermal map during the procedure may result in unintended heating of non-targeted tissues, which may cause permanent injury.
- Prior to the delivery of the first sonication and throughout the treatment, the beam path should be evaluated to avoid scars or other irregularities in the skin which can cause pain or skin burns.
- Do not use on area with impendent fracture or in close vicinity, (less than 1cm), to nerves or hollow viscera.
- Nerves can absorb heat from the adjacent bone or fat that can result in nerve injury. If a nerve is in the beam path for one or more sonications, change the tilt of the transducer to try and avoid the nerve. If the patient complains of any nerve stimulation, change the treatment plan or move the sonication.
- Failure to evaluate the ultrasound beam path prior to each sonication from the skin line to the target can result in energy delivery to critical structures anywhere along the beam path that can be painful or cause serious injury. Prior to the delivery of the first sonication and throughout the treatment, the beam path should be evaluated with great care.
- Inadequate cooling time between sonications could lead to thermal build-up that may cause serious damage to normal tissues outside the targeted volume. The cooling time between sonications should remain at all times based on the 3000-J for 90-sec cooling formula. This is managed automatically by the system software.

Refer to the Operator's Manual for the ExAblate and the MR system for more detailed warnings regarding safe use of this system.

1.3.4 Precautions

1. The physician should obtain a detailed medical history prior to treatment. Due to the period of immobilization required for the ExAblate treatment, this should include factors that may impact the risk of clotting, and assess the use of measures to minimize the risk of deep venous thrombosis.
2. Patients identified as having an intermediate or high risk for Venous Thromboembolic Disease ("VTE") should also receive prophylactic anticoagulation therapy per the National Comprehensive Cancer Network ("NCCN") guidelines for VTE prophylaxis
3. The patient should be instructed to shave all skin hair around the area that would be exposed to the ExAblate ultrasound beam. This skin area should also be wiped with alcohol immediately before treatment to remove oils to reduce the risk of skin burns.
4. Ensure that the patient has the **Stop Sonication** button before proceeding in case of emergency. Failure to do so will result in the patient not being able to stop the sonication in case of pain.
5. Ensure that patient has adequate sedation (e.g.: conscious sedation) and / or adequate level of local anesthetic (e.g.: nerve block, epidural, or similar for pain control) prior to starting the actual delivery of energy (i.e.: sonication).
6. The physician should be prepared to convert a patient to monitored anesthesia control (MAC) or general anesthesia as needed as part of the pain management protocol
7. The patient must be monitored and the level of "sedation/anesthetic" should be managed appropriately to ensure that the patient can communicate with the doctor throughout the treatment. This allows the patient immediate use of the Stop Sonication Button and/or the ability to immediately inform the doctor of any pain or discomfort during the treatment.
8. Perform geometrical verification prior to treatment to ensure accurate alignment of transducer. Failure to do so may result in inaccurate focusing of the transducer and/or result in temperatures not capable of ablating the bone tissue interface.
9. Ensure that set up interfaces (e.g.: interface between gel patient) reflection and cavitation is monitored during treatment. This may reduce the potential for adverse effects.
10. During treatment, the nominal setting of the average of energy density for all treatment is set for 9 J/mm^2 ; While the treating physician still has the ability to adjust the energy during the treatment, it should be noted that 1) lower energy densities may lead to under-treatment, 2) high energy levels requires the selection of an appropriate anesthesia regimen to ensure patient comfort.

> **Do not attempt to use components other than the ExAblate hardware, software, and system accessories, and the specified MR imaging system with the device.**

> **Do not attempt to repair the ExAblate System in the event of system failure, malfunction or any evidence of damage to the components.**
>
> **Contact InSightec technical support at 1-866-674-3874**

Refer to the Operator's Manual for both the ExAblate and the GE MR system for more detailed precautions regarding safe use of this system.

1.4 POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

The clinical study was conducted in the United States ("US"), Russia, Europe, and Canada. All study data herein is presented according to the following regional geographic cohorts:

- Non-Russian Cohort (US/OUS Combined)- refers to all study centers located in the United States, Canada, Israel and Europe.
- Russian Cohort- refers to all study centers located within Russia.

The safety analysis (**Table 1** and **Table 3**) was performed on a dataset that included all the subjects who received at least one sonication; this data includes ExAblate and sham subjects, and subjects who received sham treatment and were crossed-over to ExAblate treatment. **Table 1** presents the adverse event safety profile for the study per geographic region. In the first column of each group (i.e.: ExAblate or Sham group), the actual number of adverse events experienced is presented by body system and coded term. The second column is the number of subjects experiencing these events and the percent incidence based on the number of subjects in each treatment group as the denominator. It should be noted that the majority of all the events at all geographic regions were either mild or moderate and resolved without sequelae.

As anticipated, the Sham subjects experienced far fewer adverse events during "placebo" treatment. This is consistent across both cohorts. When comparing the events of the ExAblate treatment groups between geographic cohorts, the Russian cohort experienced significantly fewer events than the Non-Russian cohort (US/OUS Combined) (See **Table 1** for more details). Of note, under the intra-procedure "Pain/Discomfort" category events, the Russian cohort did not report any intra-procedure events. This is likely a reflection of the type of sedation/anesthesia used during the treatment procedure for patient management at these centers.

Table 1 - Frequency and Prevalence of Adverse Events by Coded Terms, by Cohort and by Treatment Group*

AE Category		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N =50		Sham N =18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
At least one AE		77	57 (69%)	1	1 (5%)	5	5 (10%)	0	0 (0%)
No AEs		0	26	0	18	0	45	0	18
Cancer Progression	Death	5	5 (6%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
Cardiovascular	Death	0	0 (0%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
	DVT	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Dermatological	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Skin Burn	0	0 (0%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
	Skin Rash	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Muscoloskeletal	Myositis	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Cognitive Impairment	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Confusion	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Neuropathy – legs	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Pain/Discomfort	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Position Pain	9	9 (11%)	1	1 (5%)	0	0 (0%)	0	0 (0%)
	Post Procedure	5	5 (6%)	0	0 (0%)	0	0 (0%)	0	0 (0%)

Table 1 - Frequency and Prevalence of Adverse Events by Coded Terms, by Cohort and by Treatment Group*

AE Category		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N =50		Sham N =18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
	Pain								
	Sonication Pain	42	40 (48%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Respiratory	Apnea	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Skeletal	Fracture	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Systemic	Fatigue	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Fever	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Urological	Blood in urine	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)

* the data of this table includes also all the rescue subjects treatment safety data

The following anticipated side effects have been identified as possible treatment related complications of MRgFUS treatment. These can be classified into Non-significant and Significant Anticipated Treatment Side Effects based on their medical severity, additional treatment required and long term consequences for the patient.

Non-significant Anticipated Treatment Side Effects of MRgFUS are those, which normally resolve without sequelae within 10-14 days of the treatment:

- Transient fever
- Oral temperature > 100.4°F/38°C
- Pain in the area of treatment.
- Transient pain in the skin.
- Swelling or firmness in the treated area
- Minor (1° or 2°) skin burns less than 2 cm in diameter
- Bruising in the treatment area

Significant Anticipated Treatment Side Effects of MRgFUS are those which may require medical treatment, may have sequelae, and for which time of resolution is not defined:

- Necrosis of tissue outside the targeted volume due to heat conduction from heated bone.

- Nerve damage, or loss of sensation in an area other than the treatment area.
- Hemorrhage in the treated area requiring emergency treatment.
- Skin burns with ulceration of the skin.
- Skin retraction, and scar formation.
- Venous thromboembolic events.
- Complications of conscious sedation (Cardiac, Pulmonary, Drug reactions)

Table 2 below summarizes all the potential risks to a patient from ExAblate treatment and the time course when they would most likely be observed.

Table 2 - Potential Risks to a Patient from ExAblate Treatment	
Short Term - -Day of treatment up to 2 weeks post-treatment	**Long term- Longer than 2 weeks post-treatment**
Sonication-related pain during treatment.	
Post-procedure pain	
Positional pain	
Skin burns	Scar formation from skin burn and possible numbness
Neuropathy	Possible muscle weakness, numbness and/or sensory loss.
DVT	DVT
Fever	
Fatigue	
Blood in urine or kidney or bladder infection due to urinary catheter	Kidney or bladder infection
Bruising at site of i.v.	
	Pathological fractures

In the clinical study, events that were deemed to be related to the procedure or the device include 70 events in 55 ExAblate Arm subjects (all regions combined) where relation to the device or procedure was categorized as Non-Significant Anticipated or Significant Anticipated.

Overall, the rate of adverse events in the ExAblate Arm differed between the Non-Russian (US/OUS Combined) and the Russian cohorts primarily due to pain experienced during the procedure. There were a total of 77 events in a total of 57 of Non Russian Cohort subjects (US/OUS Combined) with 48% of these events (in 40 subjects) occurring intra-procedure (Pain/Discomfort related events that were transient and stopped after treatment). By comparison, 5 Russian Cohort subjects experienced 5 adverse events and none of them were Pain related events. Also, the only subjects that experienced skin burns were in the Russian Cohort. This is likely a reflection of the type of

sedation/anesthesia used during the treatment procedure for patient management at these two geographic regions (see Table 3 below for more details).

The majority (i.e.: 57%) of all the events in both cohorts were either mild or moderate and resolved without sequelae. By contrast, 27.7% of all the events were sonication induced intra-procedure "severe" pain, and resolved on the day of treatment without sequelae.

Table 3 - Relation of Adverse Events to Device or Procedure by Coded Term, by Cohort and by Treatment Group*

AE category/Name		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N = 50		Sham N = 18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
RELATED TO DEVICE OR PROCEDURE									
Pain/Discomfort	Sonication Pain	42	40 (48%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Positional Pain	9	9 (11%)	1	1 (5%)	0	0 (0%)	0	0 (0%)
	Post-Procedure Pain	5	5 (6%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Dermatological	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Skin pain/skin burn	0	0 (0%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
	Skin rash	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Musculoskeletal	Myositis	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Skeletal	Fracture	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Neuropathy - leg	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Systemic	Fatigue	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Fever	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)

Urological	Blood in Urine	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Subtotal of device or procedure related events		68	53 (64%)	1	1 (5%)	2	2 (4%)	0	0 (0%)
UNRELATED TO DEVICE OR PROCEDURE									
Cancer Progression	Death	5	5 (6%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
Cardiovascular	Death	0	0 (0%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
	DVT	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Cognitive Impairment	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Confusion	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Respiratory	Apnea	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Subtotal of Unrelated Events		9	9 (11%)	0	0 (0%)	3	3 (6%)	0	0 (0%)
TOTAL ALL EVENTS		**77**	**57 (69%)**	**1**	**1 (5%)**	**5**	**5 (10%)**	**0**	**0 (0%)**

* the data of this table includes also all the rescue subjects treatment safety data

A total of 71 subjects (53% overall - 26 Non-Russian US /OUS subjects; 45 Russian subjects) experienced no adverse event at all. Of all adverse events experienced that were related to device or procedure, 42 events in 40 subjects (48%, Non-Russian US/OUS cohort) were related to the transient sonication-related procedure pain that resolved by the end of the procedure. Nine (11%) events in 9 Non-Russian US/OUS cohort) subjects were related to positional pain and all other events were less than 6% by category.

There were no unanticipated adverse device effects in this study for subjects in either the ExAblate-treated or Sham-treated groups.

Overall, a total of four Significant Anticipated events occurred including one event of skin burn (third degree burn of 3 cm area), one event of leg neuropathy (leg pain after treatment), and two events of fracture (inherent complication of bone metastases regardless of their treatment or non-treatment).

One serious adverse event reported as "possibly" related to the device or procedure was reported in this study. Three weeks after the ExAblate procedure the subject twisted their foot and experienced a pelvic fracture. Bone fractures are known and frequent

complications of the disease process for bone metastases; fractures can also result from radiation therapy which may have been a pre-study failed therapy. Although this event was likely an expected result of disease progression and twisting of the leg, the potential involvement of treatment cannot be entirely ruled out. Thus, this fracture was classified as possibly device related.

Nine additional serious adverse events in nine ExAblate Arm subjects were reported as unrelated to treatment and related to progression of the subject's cancer or other causes in one case. Seven of these events were progression of cancer that resulted in death, and one other death resulted from a heart condition. The ninth event was of a subject experiencing cognitive impairment due to a brain metastasis.

1.5 SUMMARY OF PIVOTAL CLINICAL STUDY

1.5.1 Study Design

The pivotal study was a prospective, randomized (3:1), 2-arm, sham-controlled, multicenter, international clinical study with a sham-crossover option to assess the safety and effectiveness of an ExAblate thermal ablation treatment as compared to a sham/placebo treatment to reduce/relieve the pain of metastatic bone tumors in patients who were not suitable candidates for radiation therapy.

Subjects with intractable pain from a well-defined tumor site in bone (metastasis or multiple myeloma) who refuse available treatments for pain alleviation, or who have received radiation without adequate relief from metastatic bone pain, or those for whom the physician would not prescribe radiation or additional radiation treatments were recruited into the study at 17 United States (US) and outside US (OUS) clinical sites.

Immediately following screening and optimization of their pain medications, subjects were randomized at a 3:1 ratio to either ExAblate treatment arm or sham control arm and preceded to MR screening and geometric target verification where further subjects were ruled ineligible for study participation.

Subjects who were randomized to sham treatment arm and passed the Screen Fail criteria underwent a sham ExAblate treatment with sonication energy disabled. Sham treatment did not include sedation. Subjects randomized to ExAblate treatment arm and passed the Screen Fail criteria preceded in normal fashion to ExAblate treatment at the same session.

Four test sonications were delivered. If a subject discontinued prior to the fourth sonication, they were considered a screen failed subject. All other subjects completed the planned active ExAblate treatment up to a maximum of 180 minutes sonication time.

Subject accrual lasted 46 months and subjects were followed for at least 3 months after their treatment. The final analysis included data from 125 subjects randomized to the ExAblate treatment arm and 41 subjects randomized to the sham treatment arm. Subjected were treated between March, 2008 and June, 2012. The database for this PMA reflected data collected through June 7, 2012.

Eligibility Criteria

The inclusion and exclusion criteria for the ExAblate bone mets pivotal study are listed below:

Inclusion Criteria

- Men and women age 18 and older
- Patients who are able and willing to give consent and able to attend all study visits
- Patients who are suffering from symptoms of bone metastases and are radiation failure patients:
  - Radiation failure candidates are those who have received radiation without adequate relief from metastatic bone pain as determined by the patient and treating physician, those for whom their treating physician would not prescribe

radiation or additional radiation treatments, and those patients who refuse additional radiation therapy.

- Patients who refuse other accepted available treatments such as surgery or narcotics for pain alleviation.
- Patient with NRS (0-10 scale) pain score ≥ 4 irrespective of medication
- Targeted tumor(s) are ExAblate device accessible and are located in ribs, extremities (excluding joints), pelvis, shoulders and in the posterior aspects of the following spinal vertebra: Lumbar vertebra (L3 – L5), Sacral vertebra (S1 – S5)
- Targeted tumor (treated) size up to 55 cm^2 in surface area
- Patient whose targeted (treated) lesion is on bone and the interface between the bone and lesion is deeper than 1-cm from the skin.
- Targeted (treated) tumor clearly visible by non-contrast MRI, and ExAblate MRgFUS device accessible
- Able to communicate sensations during the ExAblate treatment
- Patients on ongoing chemotherapy regiment for at least 1 month at the time of eligibility with pain NRS of the targeted lesion that is:
  - Stable over a period of at least 2 weeks prior to ExAblate treatment. Stability is defined as variation in worst pain NRS not bigger than 2 points
    AND
  - Worst pain NRS still >= 4
    AND
  - Do NOT plan to initiate a new chemotherapy for pain palliation should be eligible for the study.
- No radiation therapy to targeted (most painful) lesion in the past two weeks
- Bisphosphonate intake should remain stable throughout the study duration.
- Patients will have from 1 to 5 painful lesions and only the most painful lesion will be treated.
- Patients with persistent distinguishable pain associated with 1 site to be treated (if patient has pain from additional sites, the pain from the additional sites must be evaluated as being

Exclusion Criteria

- Patients who either
  - Need surgical stabilization of the affected bony structure (>7 fracture risk score)
    OR
  - Targeted tumor is at an impending fracture site (>7 on fracture risk score)
    OR
  - Patients with surgical stabilization of tumor site with metallic hardware
- More than 5 painful lesions, or more than 1 requiring immediate localized treatment
- Targeted (treated) tumor is in the skull
- Patients on dialysis
- Patients with life expectancy < 3-Month

- Patients with an acute medical condition (e.g., pneumonia, sepsis) that is expected to hinder them from completing this study.
- Patients with unstable cardiac status including:
  - Unstable angina pectoris on medication
  - Patients with documented myocardial infarction within six months of protocol entry
  - Congestive heart failure requiring medication (other than diuretic)
  - Patients on anti-arrhythmic drugs
- Severe hypertension (diastolic BP > 100 on medication)
- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations (weight >250 pounds), etc.
- Patients with an active infection or severe hematological, neurological, or other uncontrolled disease.
- Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease
- KPS Score < 60
- Severe cerebrovascular disease (multiple CVA or CVA within 6 months)
- Individuals who are not able or willing to tolerate the required prolonged stationary position during treatment (approximately 2 hours)
- Target (treated) tumor is less then 1cm from nerve bundles, bowels or bladder.
- Are participating or have participated in another clinical trial in the last 30 days
- Patients initiating a new chemotherapy regime, or radiation (for the targeted most painful lesion) within the last 2 weeks
- Patients unable to communicate with the investigator and staff.
- Patients with persistent undistinguishable pain (pain source unidentifiable)
- Targeted (treated) tumor surface area ≥ 55 cm^2
- Patient whose bone-lesion interface is < 1-cm from the skin
- Targeted (treated) tumor NOT visible by non-contrast MRI
- Targeted (most painful) tumor NOT accessible to ExAblate
- The targeted tumor is less than 2 points more painful compared to other painful lesions on the site specific NRS.

1.5.2 Patient Treatment

Patients who were randomized to sham treatment underwent a sham ExAblate treatment with the sonication energy output disabled. No more than 50% of the planned sonications were to be performed and the entire procedure was to last only approximately 30 minutes. Sham treatment did not include sedation, although anesthesia was permitted to alleviate, for example, pain due to positioning.

Patients randomized to active treatment underwent pre-treatment planning. Any patient deemed not to have a device accessible lesion or who received fewer than 3 therapeutic sonications was considered a screen failure and was exited from the study. If the subject remained eligible, i.e., the lesion was device accessible and they could tolerate 4 therapeutic sonications, the patient had analgesia and sedation or other measures

administered to reduce pain and limit patient motion, and the planned treatment for a maximum of 180 minutes sonication time.

1.5.3 Study Follow-up

Both active and sham treatment patients were seen for follow-up at 1 and 3 days, 1 and 2 weeks and 1, 2, and 3 months. Subjects were evaluated for general health, efficacy measurements as well as for device/procedure related AEs that occurred during the follow-up period.

Following the Week 2 visit, study subjects in both arms who were Non-responders at two consecutive visits or experienced an intolerable increase in pain or medication usage were eligible to exit from the study to pursue other treatments. Sham Arm subjects who are non-responders were permitted to opt for a cross-over treatment with the ExAblate. All patients who opted for cross-over were followed in a rescue arm for 3 months, like the active treatment group. **Table 4** provides the full schedule of evaluations in the study.

Table 4 - Patient Follow-up Schedule

	Window Allowance	**Imaging**	**Questionnaires**	**Additional data**
Enrollment (Randomization)	N/A	CT	PE,NRS,BPI, EQ-5D,KPS	Freq and dose analgesics. Economic data
Run-in Visit			NRS,BPI,KPS EQ-5D	Freq and dose analgesics
Visit #1 Baseline MR Imaging and Test or Sham Rx	On Run-in or within 1-week ±3 days of Run-in	MR	NRS,BPI,KPS, EQ-5D, Patient blinding	Freq and dose analgesics
Visit #2(phone): 1-day post Rx	N/A		NRS,BPI,KPS,OTE, EQ-5D.	Freq and dose analgesics
Visit #3(phone): 3-day post RX	±1 day		NRS,BPI,KPS,OTE, EQ-5D	Freq and dose analgesic
Visit #4(office) 1-week post Rx	±3 days		PE,NRS,BPI,OTE EQ5-D, KPS	Freq and dose analgesic. Economic data
Visit #5 (phone):	± 3 days		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesic

Table 4 - Patient Follow-up Schedule				
	Window Allowance	**Imaging**	**Questionnaires**	**Additional data**
2 weeks post Rx Visit #6 (office): 1month post-Rx	± 1 week		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesics. Economic data
Visit #7 (office): 2 month post Rx	±2 weeks		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesic. Economic data.
Visit #8 (office): 3 month post Rx	±2 weeks	MR,CT	PE,NRS,BPI,OTE, KPS, EQ-5D	Freq and dose analgesic. Economic data

1.5.4 Study Endpoints

Safety Endpoint

The safety of the ExAblate was determined by an evaluation of the incidence and severity of device-related adverse events and serious adverse events from treatment day through the Month 3 post-treatment time point.

Primary Effectiveness Endpoint

The primary endpoints were two-fold as follows:

- A clinically relevant threshold of at least 50% of ExAblate-treated patients in the ExAblate Arm will achieve 2 points or more improvement in the worst pain NRS score from Baseline at the 3-Month time point post ExAblate treatment without increase in medication.
- The response rate in the ExAblate-treated group was significantly greater than the response rate in the Sham-treated group.

The primary success criteria used a combination of the above study variables, utilizing the NRS determination of pain at Month 3 as compared to Baseline (success > 2 points or greater reduction in pain score) AND medications usage (success = no significant increase in pain meds intake within <25% difference from baseline) as the definition of Responder for study success to be declared. Those that failed either or both criteria were categorized as a Non-Responder. The success criteria were that at least 50% of the ExAblate group was

categorized as a Responder AND the % response in the Treated Arm was significantly higher than the Sham Arm.

Secondary Effectiveness Endpoint

- NRS score (measured separately from Responder/Non-responder definition for the primary endpoint)
- Medication Use quantified by "morphine equivalent usage" (measured separately from Responder/Non-responder definition for the primary endpoint)
- Quality of life (QoL) as measured by BPI-QoL
- Self assessed Overall Treatment Effect (OTE) measured items
- Self assessed EQ-5D for function and well-being subscales

1.5.5 Study Statistical Analysis Plan And Analysis Population

1.5.5.1 Study Sample Size

The proposed sample size of 148 subjects for the study was designed to reflect the two-fold primary endpoint:

- The response to ExAblate treatment is clinically relevant, and
- The response to ExAblate treatment is significantly greater than the Sham group effect.

The sample size did include the allowance for a 20% dropout rate. The sponsor did plan an interim analysis after 116 patients were randomized, 88 treatment and 28 controls, and 107 are considered by the sponsor as part of the effectiveness analysis.

1.5.5.2 Study Analysis Population

The following analysis populations were used to evaluate study results: .

Intent-to-Treat (ITT) Population

The ITT population included all randomized subjects receiving treatment (Test or Sham). Subjects receiving three therapeutic sonications or fewer, over all their treatment sessions (one or two), were considered Screen Failures (as allowed by protocol) and excluded from this analysis set.

Per Protocol Imputed Population (PPI)

The PPI population is a subset of the ITT Analysis Set of subjects who had both valid baseline measurements and at least one valid post-baseline measurement at the Day-3 visit or later for the following parameters:

- Numerical Rating Scale (NRS)
- Medication Use quantified by "morphine equivalent units"

Safety Population

The Safety population included all subjects for whom any sonication was performed (ExAblate or Sham) at any stage of the study.

Per Protocol Completers Population (PPC)

The PPC population is a subset of PPI analysis population of subjects who had observed primary efficacy analysis data at three months or discontinued prior to three months due to non-response.

Rescue Population

The Rescue population included all subjects who entered the Rescue stage of the trial.

1.5.6 Study Subject Accountability

For the pivotal clinical study, 197 subjects were screened from all geographic regions. Of these, 31 subjects were initial screening failures based on the initial review of inclusion and exclusion criteria. 166 randomized subjects were available for analysis. Of these, 14 subjects were screening failures after MRI review and 152 initiated treatment; these are referred to as the Safety Group Population. Of these, 5 subjects, all at the non-Russian sites (US/OUS Combined), did not receive more than three sonications and, thus, were screening failures per the study protocol. In addition, 5 of the remaining subjects, all at the Russian sites, had been inadvertently enrolled into a second round of treatment in the study. Thus, data from the second round of treatment for those subjects was included in the safety analysis, but excluded from the efficacy analysis, although the data from the first round of treatment was included in both analyses. Thus, 139 subjects are available for the efficacy analysis; these are the Intent-to-Treat (ITT) subject population.

1.5.7 Study Demographics And Baseline Characteristics

All study data is presented according to the following regional geographic cohorts:

- Non-Russian Cohort (US/OUS Combined) - refers to all study centers located in the United States, Canada, Israel and Europe.

- Russian Cohort- refers to all study centers located within Russia.

Baseline and demographic data for the study are reported by cohort in **Table 5**. The Baseline and Demographic population is composed of all subjects who passed initial screening criteria and received even one sonication. It is observed that the Russian cohort overall was younger that the other cohorts. The Russian cohort had a greater percentage of females. The differences in racial distribution demonstrate the multi-racial mix within the United States as opposed to that of other countries. The Russian cohort had statistically significantly smaller tumors, fewer tumors, less time since being diagnosed with bone metastases, took fewer pain medications, and had higher baseline quality of life and KPS scores.

Table 5 - Demographic and Baseline Characteristics by Cohort and by Treatment Group

Variable	Non Russian Cohort (US/OUS Combined Cohort)		Russian Cohort	
Treatment Arm	ExAblate	Sham	ExAblate	Sham
Age (yrs± SD)	63.2 ± 12.0	60.6 ± 10.4	53.9 ± 13.9	56.7 ± 10.8
Median	63.7	59.7	53.7	58.5
N	71^	19	43	18
BMI (kg/m2 ± SD)	26.1 ± 5.3	26.2 ± 3.5	26.2 ± 4.8	26.8 ± 4.7
Median	25.1	25.6	25.6	27.3
N	71^	19	43	18
Average height (cm ± SD)				
Median	167.8 ± 9.6	165.2 ± 10.0	164.0 ± 7.7	164.3 ± 6.3
N	167.5	160.0	164.0	164.0
	71^	19	43	18
Average weight (kg ± SD)				
Median	73.6 ± 15.4	71.6 ± 12.5	70.1 ± 11.8	72.5 ± 13.2
N	73.3	69.8	70.0	75.0
	71^	19	43	18
Gender				
Males	42 (58.3%)	5 (26.3%)	9 (20.9%)	2 (11.1%)
Females	30 (41.7%)	14 (73.7%)	34 (79.1%)	16 (88.9%)
N	72	19	43	18
Race				
White	64 (88.8%)	17 (89.5%)	43 (100.0%)	18 (100.0%)
Hispanic	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	3 (4.2%)	2 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (1.4%)	0 (10.5%)	0 (0.0%)	0 (0.0%)
N	72	19	43	18
Mean Tumor Volume	177.6 ± 234.4	219.0 ± 522.0	97.4 ± 160.8	68.0 ± 69.1

(cm^3)				
N	68**	19	43	18
Baseline NRS (Mean ± SD)	7.3 ± 1.7	7.9 ± 1.2	6.4 ± 1.4	5.6 ± 1.1
N	72	19	43	18
Baseline BPI-QoL (Mean ± SD)				
Physical Functioning	6.19 ± 1.89	6.45 ± 2.23	4.68 ± 1.77	3.96 ± 1.58
Affective Functioning	6.79± 2.07	707± 2.28	5.03± 1.65	4.46± 1.48
N	5.78± 2.41	6.23 ± 2.79	4.29 ± 2.12	3.54 ± 1.81
	72	19	43	18
KPS Score (Mean ± SD)	77.2 ± 8.6	76.3 ± 10.7	80.2 ± 3.4	81.1 ± 3.2
N	72	19	43	18
Pain Medication Use				
(MEDD ± SD)	45.1 ± 76.2	74.6 ± 190.2	0.9 ± 2.5	0.6 ± 0.9
Median	12.6	13.5	0.0	0.2
N	69*	19	43	18

^ Age, BMI, height and weight are missing for one subject.

*Medication usage was missing for 3 subjects.

**One or more dimensions for tumor volume was missing for 4 subjects.

Table 6 below shows the cancer characteristics between the study groups by cohort and treatment arms. The higher incidence of breast cancer in the Russian Group reflected the greater percentage of women in that group.

Table 6 - Cancer Characteristics by Cohort and By Treatment Arm

Variable	Non Russian Cohort (US/OUS Combined Cohort)		Russian Cohort	
	ExAblate N = 72	Sham N = 19	ExAblate N = 43	Sham N = 18
Primary Cancer Type				
Breast	12 (16.7%)	7 (36.8%)	25 (58.1%)	14 (77.8%)
Prostate	14 (19.4%)	1 (5.3%)	1 (2.3%)	1 (5.6%)
Kidney	8 (11.1 %)	2 (10.5 %)	1 (2.3 %)	0 (0.0 %)
Lung	11 (15.3%)	3 (15.8%)	6 (14.0%)	1 (5.6%)
Multiple myeloma	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	24 (33.3%)	6 (31.6%)	10 (23.3%)	2 (11.1%)
....Missing	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lesion Type				
Osteolytic	39 (54.2%)	11 (57.9%)	21 (48.8%)	10 (55.6%)
Osteoblastic	22 (30.6%)	3 (15.8%)	3 (7.0%)	3(16.7%)
Mixed	10 (13.9%)	5 (26.3%)	19 (44.2%)	5 (27.8%)
Missing	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Target Tumor Location				
Coccyx	1 (1.4%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Acetabulum	8 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Femur	2 (2.8%)	1 (5.3%)	2 (4.7%)	2 (11.1%)
Humerus	2 (2.8%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Ilium	28 (38.9%)	7 (36.8%)	15 (34.9%)	8 (44.4%)
Ischium	5 (7.0%)	1 (5.3%)	7 (16.3%)	2 (11.1%)
Pubic Ramus	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rib	9 (12.5%)	3 (15.8%)	9 (20.9%)	2 (11.1%)
Sacroiliac	1 (1.4%)	2 (10.6%)	4 (9.3%)	0 (0.0%)
Sacrum	8 (11.2%)	3 (15.8%)	3 (7.0%)	2 (11.1%)
Scaula	5 (6.9%)	0 (0.0%)	2 (4.7%)	2 (11.1%)
Sternum	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Time from Initial Diagnosis of the Bone Metastasis (Yrs)	1.7 ± 2.2	1.7 ± 1.6	0.7 ± 1.8	0.8 ± 2.3
N	69*	19	43	18

Number Bone Metastatic Lesions ± SD **Median** **Range** **N****	2.5 ± 1.8 2 (1-10) 52	1.9 ± 1.0 2 (1-4) 14	1.6 ± 1.6 1 (1-10) 34	1.6 ± 1.3 1 (1-6) 16
Number of Distinguishable Painful Lesions **Median** **Range** **N**	1.4 ± 0.8 1 (1-4) 72	1.6 ± 0.8 1 (1-3) 19	1.0 ± 0.2 1 (1-2) 43	1.1 ± 0.2 1 (1-2) 18
*Date of Initial Diagnosis was missing for 2 subjects ** missing patients had unknown number of lesions				

Treatment differences are presented in **Table** 7 by geographic cohort. "EDBS" is the level of energy density delivered to the bone/tumor interface which is summed across all sonications and determined post-treatment.

Table 7 - Treatment Characteristics by Cohort for ExAblate Arm		
	Non Russian Cohort (US/OUS Combined)	**Russian Cohort**
EDBS (J/mm^2) (Mean +/- SD)	4.5 + 3.0	6.9 + 2.8
Intra-procedure Sonication Pain (percent AE)	37%	0%
Mean Time Inside Scanner (min) (Range)	175.8± 62.2	126.4.4± 47.4
Mean Sonication Treatment Time (min) (Range)	78.1± 48.5	54.5± 38.8
Mean Intra-Procedure Oxygen Saturation (Range)	97.4± 2.4	96.1± 2.4
Sedation Method	Local/Conscious Sedation	Complete

1.5.8 Study Results

1.5.8.1 Primary Effectiveness Endpoint

The ITT efficacy analysis was conducted on the group of subjects who met treatment criteria of at least 4 sonications per protocol. Subjects were considered "Responders" if they demonstrated at least a 2-point improvement on the 0-10 pain Numerical Rating Scale (NRS) from Baseline to Month 3 and no more than a 25% increase in opioid pain medical intake (in units of morphine equivalents).

Primary endpoint responders of Table 8 show greater improvement in the ExAblate arm than Sham arm in both geographic cohorts. The Russian Cohort had the highest responder rate in the ExAblate Arm, 90%, which was significantly greater than for the Russian subjects in the Sham Arm, 13% ($p<0.0001$). The Non-Russian Cohort (US/OUS Combined) ExAblate responder rate was 55%, significantly greater than the 26% responder rate in the Sham ($p=0.04$) and is very close to that assumed *a-priori* in the protocol for calculating power. The ExAblate responder rates were strong in both geographic cohorts, (approximately twice that of Sham responder rates).

The statistical significance of the effectiveness in non-Russian subjects is highly sensitive to assumptions about missing data, but when considering data across geographic cohorts, then the data is quite robust.

Table 8 - Proportion of Responders by Geographic Cohort and Treatment Group				
Site	**N**	**% Responders (n/N)**		**p-value**
		ExAblate	**Sham**	
Non-Russian Cohort (US/OUS combined)*	83	55% (35/64)	26% (5/19)	0.04
Russian Cohort	56	90% (36/40)	13% (2/16)	<0.0001

* This analysis is based on the agreed upon ITT population. However, if the analysis includes subjects in screening failure 3 group (see Table 8), the result for the non-Russian cohort is as follows:
N=88, % ExAblate Responders=51% (35/69), % Sham responders=26% (5/19).

It should be noted that the ExAblate was already marketed in Russia for pain palliation of metastatic bone cancer at the time of this clinical trial. Russian investigators were more likely to use a patient management approach that involved deeper sedation/anesthesia which permitted them to respond to the real time thermal feedback to achieve thermally ablative temperatures at the bone/tumor interface without patient complaint. Physician training will emphasize the need for adequate pain control to permit the treating physician to utilize the appropriate energies in response to the real time thermal feedback to achieve ablative temperatures at the bone/tumor interface.

1.5.8.2 Secondary Effectiveness Endpoints

1.5.8.2.1 *Quality of life (QoL)*

As shown in **Table 9**, the quality of life (BPI-QoL) secondary analyses, show significantly greater improvement in the ExAblate Arm than Sham Arm at all geographic regions. Furthermore, all geographic regions show a mean change from baseline in the ExAblate Arm was greater than 2 points over Sham Arm, indicating that the improvement was clinically significant.

Table 9 - BPI-QoL by Geographic Cohort and Treatment Arm				
Cohort	**N**	**Change From Baseline**		**p-value**
		ExAblate	**Sham**	
Non-Russian Cohort (US/OUS combined)	83	2.19	0.74	0.048
Russian Cohort	56	2.66	-0.48	<0.0001

Note: A change of 1 points on the BPI-QoL is clinically significant; the "-" sign indicate worsening of QoL

The overall BPI average score in the ExAblate treated group decreased from 5.7 at baseline to 3.6 at the 2 Week visit and remained at 3.3, 3.1 and 3.3 at the 1 Month through 3 Month visits respectively. The baseline average BPI for the Sham control group was 5.7 at baseline and 4.7, 4.6 and 5.0 at the 1 Month through 3 Month visits respectively.

1.5.8.2.2 *Numerical Rating Score "NRS"*

As shown in Table 10 below, NRS scores also showed greater improvement in ExAblate Arm than Sham Arm at all geographic regions, with results reaching significance in the Non-Russian Cohort (US/OUS combined) and Russian Cohort. In all cohorts, ExAblate Arm mean improvement was above the 2-point threshold for clinical significance, while in none of the cohorts was Sham Arm close to clinical significance.

Table 10 - Numerical Rating Scale by Geographic Cohort and Treatment Group

Sites	N	Change From Baseline		p-value
		ExAblate	Sham	
Non-Russian cohort (US/OUS combined)	83	3.17	1.32	0.04
Russia cohort	56	4.80	0.13	<0.0001

Note: A change of 2 points on the NRS is clinically significant.

1.5.8.2.3 *Pain Medication Use*

Opioid pain medication use, measured in morphine equivalent daily dose, was one of the composite measures for determining Responder status in the primary efficacy endpoint (Table 11). All Responder subjects stopped, reduced, or maintained their medication usage. These results were observed while the subjects also demonstrated a clinically significant reduction in pain (2 or more points on the NRS).

Table 11 - Opioid Medications Use at Month 3 Compared to Baseline for all Responder ExAblate Subjects by Cohort				
	Non-Russian Cohort (US/OUS combined)		Russian Cohort	
	N = 35		N = 36	
	N	%	N	%
Pain Meds Stopped	10	29%	9	25%
Pain Meds Reduced	10	29%	2	6%
No Change in Pain Meds	15	43%	25	69%
Total	35	100%	36	100%

When comparing the Pain Medications Use in Morphine Equivalent Units by Time Point in the ITT Population for sham and test groups, the result favors treatment as these patients did not increase their pain medication requirements.

Seventeen Sham subjects opted to receive a Rescue treatment using the ExAblate. Of these 17 subjects, 13 were considered Responders to ExAblate treatment (76.5% Responder rate, Rescue Arm) while 4 were Non-Responders. These subjects were unblinded, but the result here shows a similar pattern to the blinded portion of the study. All adverse events experienced by the Rescue subjects were included in the safety analysis.

1.5.8.2.4 *Overall Treatment Effect (OTE)*

Overall treatment effect measured the subject's opinion of the effect (better, same, worse) the treatment has had on their well-being. The question asks the subject to rate this as compared to their last visit, not with baseline or pre-treatment.

In general, the ExAblate Arm showed continuing improvement visit to visit until it begins to stabilize by Month 3. The Sham subjects generally showed No change or Worsening from Week 1 through Month 3 with Worsening becoming more evident.

1.5.8.2.5 *EQ-5D*

This study utilized the descriptive component of the EQ-5D for the five subscales of mobility, self care, usual activities, pain/discomfort and anxiety/depression.

The ExAblate Arm showed clinically significant improvements in all 5 categories. The Sham, in contrast, showed subjects mostly stayed the same and 15-23% actually worsened in a category. All of the questionnaire items except for mobility demonstrate greater improvement in health in the ExAblate Arm than in the Sham Arm as compared to Baseline, particularly the later in time the assessment was performed.

1.5.8.2.6 *Study Rescue Population*

Seventeen Sham subjects opted to participate in a Rescue treatment using the ExAblate. Of these 17 subjects, 13 were considered Responders to treatment (76.5% Responder rate, Rescue Arm) while 4 were Non-Responders. These subjects were un-blinded, but the result here shows a similar pattern to the blinded portion of the study. All adverse events experienced by the Rescue subjects were included in the safety analysis (Tables 2 and 3) presented previously.

1.6 CONCLUSIONS DRAWN FROM THE STUDIES

1.6.1 Effectiveness Conclusions

The results of the present analyses provide reasonable assurance of efficacy and meet the pre-specified criteria for success. The Russian Cohort had the highest responder rate in the ExAblate Arm, 90% (36 subjects), which was significantly greater than for the Russian subjects in the Sham Arm, 13% (2 subjects) ($p<0.0001$). The Non-Russian Cohort (US/OUS Combined) ExAblate responder rate was 55% (35 subjects), significantly greater than the 26% (5 subjects) responder rate in the Sham ($p=0.04$). The ExAblate responder rates were strong in both geographic cohorts, and are much greater than the study hypotheses of the clinically relevant threshold of at least 50%.

When looking at the secondary endpoints, measuring quality of life issues, there was an improvement seen in all variables favoring the treated group.

It is noted that only one patient with multiple myeloma was treated in this trial and it was reported as a non-responder. With this information, it is difficult to determine what the effect of this device may have in this sub-population. Further study is needed to determine if this device is safe and effective for this subpopulation.

1.6.2 Study Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The most commonly reported AE was due to pain with treatment. There were a total of 77 events in a total of 57 Non-Russian Cohort

subjects with 48% of these events (in 40 subjects) occurring intra-procedure (Pain/Discomfort related events that were transient and stopped after treatment). By comparison, 5 Russian Cohort subjects experienced 5 adverse events and none of them were Pain related events. The majority (i.e.: 57%) of all the events in both cohorts were either mild or moderate and resolved without sequelae. By contrast, 27.7% of all the events were sonication induced intra-procedure "severe" pain, and resolved on the day of treatment without sequelae. By contrast, 27.7% of all the events were sonication induced intra-procedure "severe" pain, and resolved on the day of treatment without sequelae. Also, the only subjects that experienced skin burns were in the Russian Cohort.

A total of four Significant Anticipated events occurred including one event of skin burn (third degree burn of 3 cm area), one event of leg neuropathy (leg pain after treatment), and two events of fracture (inherent complication of bone metastases regardless of their treatment or non-treatment).

One serious adverse event reported as "possibly" related to the device or procedure was reported in this study. Eight deaths in ExAblate Arm subjects were reported as related to progression of the subject's cancer or other causes in one case, and unrelated serious adverse events to treatment.

There were no unanticipated adverse device effects in this study for subjects in either the ExAblate-treated or Sham-treated groups.

1.6.3 Study Overall Conclusions

For this population of patients suffering from bone pain due to metastatic disease, who are failures of standard radiation therapy, or who are not candidates for radiation, or who refuse radiation therapy, the ExAblate treatment is a reasonable alternative to existing treatments. The result from the pivotal study appears efficacious and the safety profile is reasonable and does not cause any increased risks for this population already at significant risk due to the underlying disease process.

In conclusion, the treatment benefits of the device for the target population outweigh the risks of diseases when used in accordance with the directions for use.

2.0 SAMPLE PATIENT LETTER

ExAblate MR Guided Focused Ultrasound for the Palliative Treatment of Bone Mets

What Patients Should Know

You have been scheduled for a magnetic resonance guided focused ultrasound ("MRgFUS") treatment for your painful bone metastasis. Your treatment appointment has been scheduled for _____ AM / PM.

If your appointment is in the morning, please do not eat or drink anything after midnight the night before the procedure. If your appointment is after noon, do not eat or drink anything after 6:00 AM.

Because we need good contact between the ultrasound and the area where your bone metastasis is location, we would like you to shave that area the night before or morning of the appointment. Please do not apply any talcum powder or cream or oil(s) to your area of bone metastasis before the treatment appointment. If you have scars, please show them and, if possible, mark your scars with the supplies given to you on the morning of the appointment.

The InSightec ExAblate system that will be used by your doctor is a MRgFUS system. The MRgFUS uses information from magnetic resonance ("MR") images and your sensations during the treatment to monitor the safety and success of the treatment.

As a patient undergoing this treatment your role in this process is very important. The following information is for you to read prior to starting the treatment. Should you need further information, do not hesitate to ask your treating physician any questions you may have.

On the day of your treatment, medicine will be given through a small tube in your arm vein (I.V.), or injection of local anesthesia at the site, or in the form of a pill to help you relax and to reduce any discomfort from the treatment. You will have a catheter placed in your urethra to help keep your bladder empty during the treatment. You will lie down on the table on your area where the bone metastasis is located, and the doctor will take an MR scan. The doctor will use the MR images to plan your treatment and control where the ultrasound waves are aimed.

During the treatment, a number of short ultrasound pulses (sonications - about a 20 second energy pulse followed by a 1 minute waiting period) will be aimed into the area of your bone metastasis to heat up the bone. This heating causes your bone to absorb the energy and heats up to damage the nerves that are naturally located on your bone. With the proper amount of heat, the nerve cells will be killed (ablated). During each sonication more MR images will be taken to see where the heating is taking place. Your doctor will

review these pictures throughout the procedure to confirm that the treatment is continuing as it should.

During treatment your vital signs (pulse, and the level of oxygen your blood is carrying) will be measured. You must lie still and not move during this time. You may experience a sore neck or discomfort from lying face down in the same position for a long time during the treatment. You may speak at any time during the treatment and your doctor will be able to hear what you say. From time to time, you will be asked how you are feeling. If you become uncomfortable you may request medication to help with the discomfort. The kind of feelings that you might experience caused *by the treatment* itself have been described by previous patients as: a moderate pain/warmth sensation at the bone metastasis location; a short sting like pain at the location of your bone metastasis. In all cases the feeling did not last more than 5-10 seconds during the energy delivery. Although these are normal sensations, you should inform your doctor so they may be addressed with medication or a change in the treatment. **However, at no time should you experience sharp pains on the skin, or at the site, or in the buttocks, along your leg(s) during the actual treatment.**

When you are positioned on the table, an Emergency Stop button will be given to you to hold during the treatment. If you press this button it will immediately stop the treatment and alert your doctor. If at any time you experience these feelings of a sharp pain during the treatment you should press the Stop Button and inform your doctor about the kind of pain that you experienced. There are several system parameters that your doctor can change to continue the treatment and eliminate your pain. If you say that it hurts too much, or if you find that it is too hard to continue the treatment, the treatment can be stopped.

As soon as the treatment is completed, you will have another MRI. Your doctor will examine these images to confirm the treatment effects. Once finished, you will be taken out of the MR, the I.V. and catheter will be removed, and you will be taken to a room while the medication from the treatment wears off. In 1–3 hours you should feel well enough to be released and assisted home. **You will need a ride home from this appointment**. We will be happy to call your ride when you are near the completion of the treatment in case they do not want to wait at the hospital for you. Please plan on spending up to 5 to 6 hours at the hospital, as sometimes there are delays.

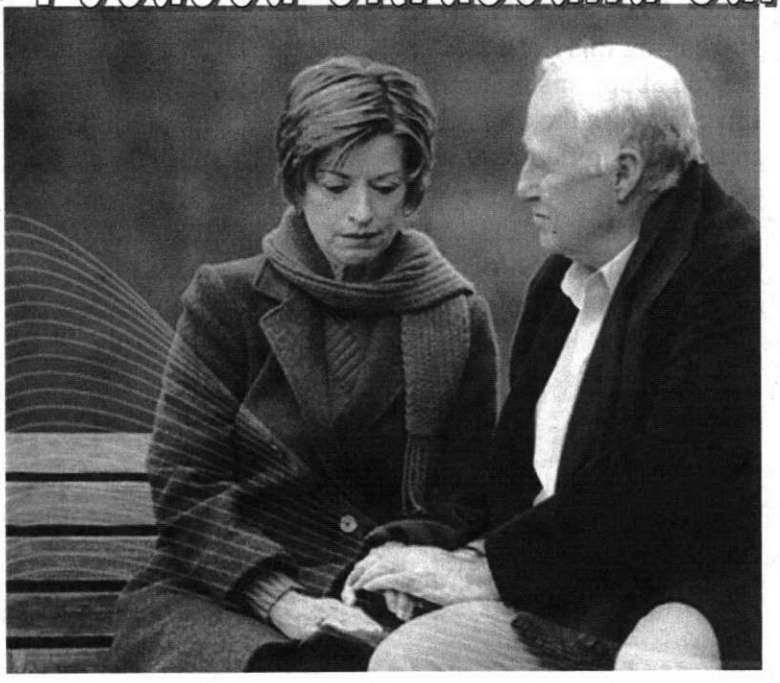
In most patients treated, if adequately medicated discomfort from the treatment is mostly related to lying prone and holding still for the period of the treatment. These effects may be helped by over-the-counter medications and should go away within a few hours.

We hope that this will help explain your treatment, and what you can expect. Please do not hesitate to ask if you have any further questions.

If you have any questions or concerns that are not answered here, you may contact your doctor at _____.

PATIENT'S MANUAL

MR Guided Focused Ultrasound Surgery



A patient's guide to ExAblate non-invasive treatment for the palliation of painful bone metastases

Table of Contents

1 Glossary

MRgFUS	Magnetic Resonance guided Focused Ultrasound Surgery
Bone Mets	abbreviated term for bone metastasis
Metastasis	Spread of main cancer to other location in the body, including to the bone
Sham / placebo	Used in a clinical trial to demonstrate effectiveness against a know standard which would be No Treatment
Randomized	Method used to assign subjects to a treatment arm of the study so that the actual treatment allocation remains unknown to participating subjects until the end of the study
Sonication	A pulse of ultrasound energy delivered over a period of 10-20 seconds.

2 What is the ExAblate MRgFUS treatment and how does it work?

Your doctor has prescribed the ExAblate MRgFUS procedure to treat your painful bone mets because you are a good candidate for the device.

The ExAblate® device uses energy that is generated by an ultrasound source (in the patient table) and where the rays of the ultrasound are focused at a specific point in the body to create a significant heating at this focus that is much higher than anywhere else. This is similar to how the sun's rays ignite a flame when focused under a magnifying glass.
The ExAblate system is fully integrated to a Magnetic Resonance imaging scanner (see **Figure 1**). The whole procedure is actually conducted inside the imaging scanner. During this procedure, the ExAblate will use the MR imaging for planning your treatment, treatment delivery guidance and therapy feedback during the treatment of the bone mets tissue.

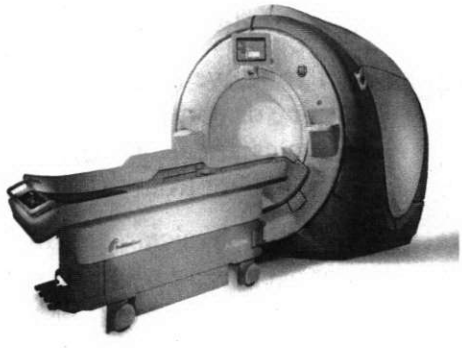


Figure 1 ExAblate Patient Table docked to the MR scanner

Ultrasound is a form of energy that passes through skin, muscle, fat and other soft tissue so no incisions or inserted probes are needed. The ultrasound energy is also non-ionized. High intensity focused ultrasound energy, when focused on a small target volume, provides a therapeutic effect by raising the tissue temperature of the target high enough to destroy it. Only tissue at the target is heated well above the temperature needed to kill the tissue.

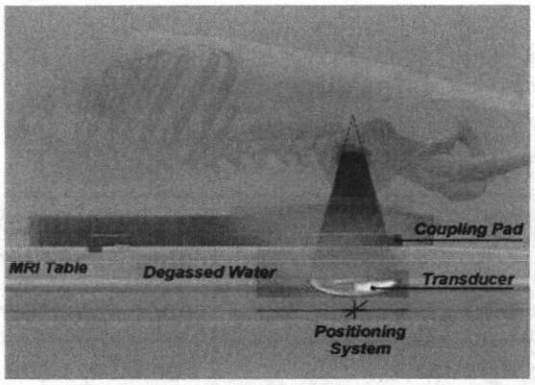


Figure 2: Visualization of the actual treatment for bone Mets with the ExAblate system

3 Why doctors use it?

Your doctor has assessed that your pain from your bone mets may have not responded to the radiation therapy, or you are not a good candidate to standard radiation, or you may have informed your doctor that you refuse radiation therapy. The ExAblate treatment is one of the therapies that may be available to your doctor to offer. Your doctor is offering the ExAblate procedure because it is non-invasive and does not use radiation as a source of heat. Based on the clinical study that served to gain FDA approval, the procedure has a very good chance to help your condition. Additionally, it may allow you to reduce your pain medications, such as narcotics with their sedative side effects, and better your quality of life.

Your doctor will be discussing the full risks and benefits of this procedure with you.

4 Am I suitable for the ExAblate treatment? – Contraindications

ExAblate MRgFUS is not suitable for all patients. Patients who have any of the following should inform their doctor so he can make good treatment choices with you.

- If you have any kind of metallic implants, such as pacemakers, neurostimulators, spine or bone fixation devices, total joints, metal clips, screws, etc. you may not be a candidate. Any metallic implants must be non-magnetic to prevent injury to the patient from the MR's strong magnetic field.
- If your physician has told you that you have a bone that is fragile and may break or needs surgery to be stabilized, or has already been stabilized with surgical implants, you may not be a good candidate. The cancer itself as well as cancer treatments may cause the bone to weaken and fracture.
- Women who are pregnant may not be treated with this device. The effect of MRgFUS on the fetus could cause permanent injury or death to the fetus if the

fetus is in or near the location of the focused MRgFUS beam. Also, the use of MR contrast agent is not advised and could potentially harm the fetus.

- Patients with mental impairment including and not limited to Alzheimer's, dementia, mental retardation, or other neurodegenerative changes, including Parkinson's disease, uncontrolled epilepsy/prone to seizures, dystonia, or like conditions
- Patients who are not generally healthy enough to withstand the treatment and to lie still in the same position for approximately 3 hours are not candidates for this treatment. These patients may have any of the following conditions: unstable heart conditions, such as a recent myocardial infarction (heart attack), congestive heart failure (fluid around the heart), unstable angina pectoris (chest pain) even on medication, etc.
- Patient with extensive skin scaring in the areas that would be treated.
- Patients with tumors in the skull
- Patient on dialysis
- Patients with an active infection or severe hematological, neurological, or other uncontrolled disease.
- Patients with severe cerebral vascular "CVA" disease (multiple CVA or CVA within 6 months)

Please discuss all these conditions with your physician so your doctor can properly evaluate your suitability for the ExAblate therapy.

5 Things you must do to avoid serious harm – Warnings

- Tell your physician if you have ever experienced allergic reactions to imaging contrast media. Patients who have allergies to MR contrast materials may not be suitable candidates. Both contrast and non-contrast images may be collected for viewing the effects of the thermal ablation. Your doctor may consider other imaging techniques to evaluate the ablation effects.
- Tell your physician of any medication allergies that you may have including and not limited to recent or past medications.
- Your physician will need to perform a full medical evaluation and full review of your medical chart to assess fully your overall condition. This is necessary to ensure a safe and effective ExAblate therapy for your condition.
- Show your physician any scar that overlies the target treatment area. Scar tissue is a different tissue type than surrounding tissue and is more susceptible to heat damage causing pain if located in the beam pathway. Alternate beam paths may be able to avoid the scar tissue.
- Patients may not be treatable when air-filled organs such as the lungs, bowel, etc. are found in the beam path and cannot be moved or maneuvered around. Focused

ultrasound can burn tissue/air surfaces in the beam path and cause perforations (tears) in these tissues.

- The interface between the ExAblate device (gel pad) and the patient' skin must be free from tissue folds, air bubbles, skin lesions, body hair and oily skin surfaces to prevent painful heat generation and skin burns. The transducer interface (gel pad and water) must be in complete contact with your skin without gaps. Your physician will monitor this area during the treatment to avoid potential skin burns.
- You will be given a Stop Sonication button before initiating treatment. In the event of pain or patient motion, activate the stop sonication button so that you will not be harmed. If you are experiencing pain, tell your physician so he can alter the treatment to avoid nerves, or alter the pathway to minimize the pain, slow the sonications down to allow for longer heat dissipation times, or provide medication to make you more comfortable. Failure to communicate this with your physician could result in serious injury. The Stop Sonication button is a safety feature built into the system for the patient.

6 Things you must do to avoid other harm – Precautions

1. Tell your physician of all medications you take and of any risks or tendencies you may have for blood clots. Due to the period of immobilization required for the ExAblate treatment, the risk of a blood clot forming can increase because you must lie still for so long during this treatment. If your risk for blood clots is high, your medical team may perform additional tests and prescribe additional medications during the procedure that may avert any potential problems.
2. You will be instructed to shave all skin hair around the area that would be exposed to the ExAblate ultrasound beam. Stubble or hair sticking above the skin surface may focus the heat on the area around the hair and result in skin burns. Your medical team will also wipe the area with alcohol immediately before treatment to remove oils to reduce the risk of skin burns
3. You **must** lie very still for the entire treatment without moving. Straps or restraints may be used to help you hold your position and prevent your moving during the treatment. You will also be given medication to increase your comfort during the treatment, or reduce any painful treatment sensation that you may experience during the delivery of the therapy.
4. You will be given a **Stop Sonication** button before the treatment starts which you will hold during the treatment. If you experience great pain or discomfort, push the button to stop the treatment and tell your physician your the problem. Your physician will be able to address your concern to alleviate the issue.
5. You will need to take medicine before and during the procedure to dull your pain and make you more comfortable during the procedure, especially as you will be lying on the painful area to be treated. The destruction of the nerves on the bone surface may be very sensitive and painful during the procedure.

The pain is generally temporary lasting only seconds after the sonication, then it dissipates. If you are experiencing significant pain that lasts longer, you need to tell your doctor so they can give you enough medication that will allow them to alter the treatment so that they may still heat the tissue to the proper temperature to kill the nerve cells..

6. Tell your physician of any medical conditions you have that could affect your ability to lie on the targeted area for long periods of time. Medical conditions could include neck or back problems (herniated discs or pinched nerves), severe arthritis, etc. Depending upon the target location, the medical personnel may be able to position you in a way to avoid aggravating these kinds of problems.

7 Risks of having this done

Infrequent complications have been reported following ExAblate MRgFUS treatments which are described below:

Short Term Risks – Day of Treatment up to 2-Weeks Post-Treatment

The most common potential risks associated with the ExAblate device and procedure is pain and discomfort (mild, moderate and severe) related to the delivery of the sonication energy (heating the nerve to temperatures hot enough to kill it) which dissipates shortly after the sonication (approximately less than 1 minute) and can be managed with judicious use of anesthetic and sedative medications administered by your physician. Occasionally, patients may experience post-procedure pain which usually resolves within a few days and may be due to irritated nerve endings as the nerve dies. Other risks include position-related pain due to the position you maintained during the entire treatment process which can appear after treatment within 1-3 days and should resolve quickly. These can be minimized by careful positioning at the procedure start to support the rest of the body in a comfortable position during the treatment.

If there is improper acoustic coupling (i.e., the interface between the body and the transducer gel pad has gaps), then there is a possibility of skin burn. These events are acute, occurring on the day of treatment with red skin patches or even 2-3 degree burns. These are minimized by ensuring the skin around the area of the treatment is free of any hair, oil based product and cleaned with alcohol prior to treatment. In addition, these events may be further minimized by communication with your doctor when you first feel skin pain. Moderate to severe skin burns should heal and fade within 7-14 days.

If a nerve was located close to the designated area for ablation or close to a bone in the far beam path, you may feel pain during sonications, or numbness, or pain immediately after the treatment or during the following few days. If you experience pain in a nearby area during the sonication, you should tell your physician so they can check for the presence of nearby nerves in the beam path.

You may experience a blood clot (also known as Deep Venous Thrombosis, or "DVT" for short) after the procedure that is not treated emergently; you may have complications related to it if it does not resolve quickly. If this were to occur, the clot could travel to other part of the body and cause heart, brain, or lung damage.

You may experience a fever within a few days after the procedure if a large amount of tissue has been ablated. If your temperature goes above 100°F for 24 hours, you should call your physician. In the clinical study for ExAblate treatment for bone metastases, this fever event occurred in one patient.

You may see blood in your urine or have a bladder or kidney infection because of the catheter used to drain your bladder during the procedure within days to a week after the procedure, but it should resolve completely. If you get a urinary tract infection, you may need antibiotics and it may take approximately 2 weeks to resolve.

You may have bruising in the area of the iv catheter following the procedure, similar to that experienced after blood draws which should resolve on their own within a week..

You may feel tired for several days after the procedure because of the exertion to remain still for so long.

Long Term Risks – Longer than 2-Weeks Post-Treatment

Overall, ExAblate MRgFUS is a reasonably safe procedure for treating painful bone metastases with minimal risk. Infrequent complications that have been reported following ExAblate treatment include the possibility of scar formation after skin burn and possible numbness. If a nerve was damaged (unintended), there may be muscle weakness, numbness, or sensory loss that may resolve after several months, or it may be non-reversible. In the clinical study for ExAblate treatment for bone metastases, this occurred in one patient treated with the ExAblate treatment.

If you experience a blood clot after the procedure that is not treated emergently, you may have long term complications related to it if it does not resolve quickly. You could have muscle, heart, brain, or lung damage.

Bone fractures may occur at any time as a result of the bone metastases weakening the bone, prior radiation therapy, or the ExAblate procedure.

8 Benefits of having this done

Fifty-five percent (55%) of the group of patients treated in the United States and Europe and 90% of the group of patients treated in Russian experienced substantial pain relief at the site of the ExAblate-treated bone mets and it usually was observed as early as 2 weeks post procedure and coincided with relatively quick improvement in quality of life. The procedure is non-invasive (i.e., not surgical scars) and may be performed in out-patient basis.

However, you may not gain any pain relief from this procedure. This procedure does not treat the underlying cancer, nor prevent the spread of new metastases or address the pain from untreated lesions which may become painful after this treatment.

9 How to decide about this treatment

You must explain all your medical conditions to your physician as well as the level of pain that you are experiencing. Your physician will evaluate whether you are a good candidate for the ExAblate treatment. Together, in consultation with your physician and caregivers, you will need to decide if you can tolerate the treatment and are a suitable

candidate. Your physician will also discuss any other treatment options that are available to you.

10 What happens before the treatment

Once you have been evaluated to see if you are a suitable candidate as described above and have explained to you all the risks associated with the device and the procedure, you may be scheduled for a CT imaging (if not available) to determine if the bone metastases location is accessible for the ExAblate as the final step. You will shave the skin over the target area and it will be cleaned. You will have a urinary catheter placed to drain your bladder during the procedure and will wear compression stockings during the procedure. Your physician may start you on medication to minimize risks of DVT. An intravenous catheter will be placed into your arm to administer fluids and medications. You will be administered medications to dull your pain and make you comfortable. You will be positioned on the table so that the target area is in direct contact with the transducer gel pad without any gaps and so that you are comfortable and supported. Your heart rate, blood pressure and blood oxygen levels will be monitored throughout the procedure.

11 What happens during the treatment?

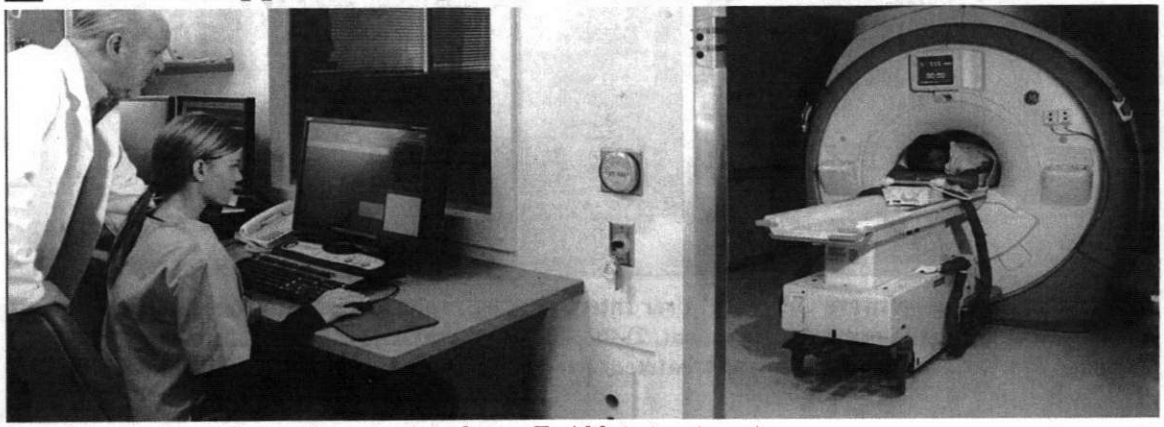


Figure 3: Picture of a treatment set up for an ExAblate treatment

You will be given a **Stop Sonication Button** to hold during the procedure. You will be moved inside the MR device (see **Figure 3**). If you get claustrophobic, tell someone so that you can receive medication to keep you calm. The procedure will be performed from a computer in the room adjoining the MR suite. A circulating nurse will be close to check on you and to administer medication.

A series of MR images is taken for the purpose of planning the treatment. The physician will mark the area to be treated and the machine will calculate and plan the treatment to identify the number of sonications needed to cover the area and the energy needed to perform those sonications and avoid vulnerable areas with nerves and blood vessels; An example of the treatment software of a typical bone ExAblate treatment is shown in Figure 4 below.

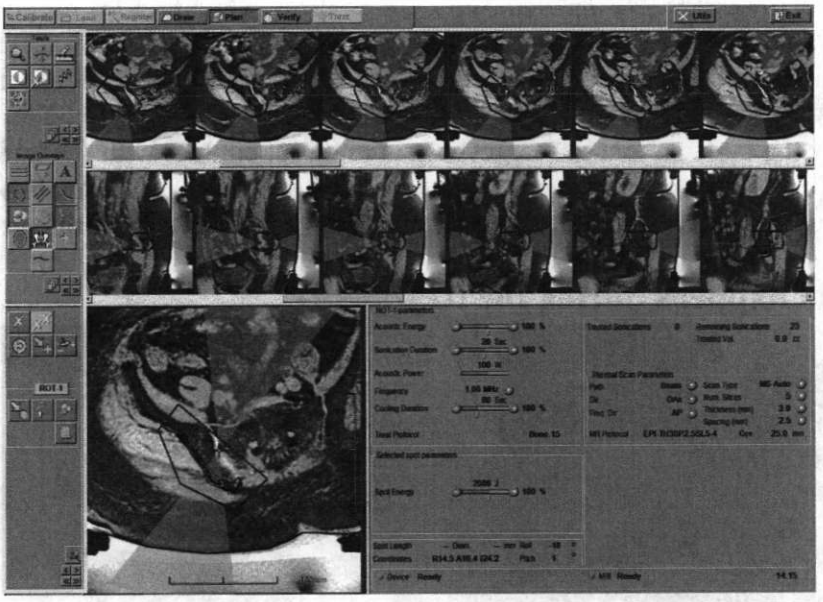


Figure 4: ExAblate Software Graphical User Interface: 1) Graphical user interface uses buttons and icons to identify functions during treatment, 2) the software overlays graphical displays on MR image(s), 3) treatment parameters and treatment progress easily accessible during treatment.

Initially, very low strength sonications are delivered to ensure that the MR and the transducer are aligned properly. After that, the sonications will be at full strength and will move sequentially over the area marked for treatment. After each sonication, the doctor will talk to you to make sure you are okay. You must remain still throughout the treatment session.

After all the sonications have been performed, a contrast agent will be administered through the IV catheter and a final series of MR pictures is obtained to see how well the treatment target was covered.

12 What happens after the treatment

You will be removed from the machine, and you will be asked to get up and walk around. Once you have been determined to be stable, all the monitoring equipment and catheters will be removed. You will be moved to recovery room for observation for 1-2 hours. Your physician will come by to evaluate you, and to explain to you the post treatment care that you may need. Your physician will let you know when you can go home, usually the same day and when you will need to return for a follow-up visit.

13 When to call your doctor

If you experience severe pain that is not relieved by the medication prescription, bleeding, or fever of 100°F or higher within 48 hours of treatment, call your physician. You may receive a follow-up phone call the next day, or you may be scheduled for a post-treatment follow-up visit.

14 Where you can find out more

If you desire more information about this procedure, please visit the sponsor's website to learn more about the device and bone mets treatment at " **us.insightec.com** ", or you may call our customer service toll-free line at **1 866-392-2528**.

15 How clinical studies were done

The pivotal study for this device was conducted under an investigational device exemptions and published on Clinicaltrials.gov (NCT00656305). This was a global study conducted at 17 centers located in the US, Canada, Israel, Rome, and Russia. The study design included randomization into a treatment arm and a placebo arm in a 3:1 ratio.

A total of 139 subjects took part in the study. The post treatment follow up was through 3 months. The primary endpoint was clinically significant pain relief and stable or reduced pain medication usage; secondary endpoints were related to improved quality of life. After 3 months follow-up, 55% of the group of patients treated in the United States and Europe and 90% of the group of patients treated in Russia experienced substantial pain relief at the site of the ExAblate -treated bone mets. This pain relief improvement coincided with improvement in quality of life. The results of the study provided strong evidence of efficacy with a very good safety profile.

InSightec –
October-2012